REMARKS

The amendment does not introduce new matter within the meaning of 35 U.S.C. §132. Accordingly, the Examiner is respectfully requested to enter the above amendments before examination.

1. Rejection of Claims 1-6 under 35 U.S.C. § 102(b)

The Official Action states that claims 1-6 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Ju (1996) for the reasons of record set forth in the Official Action dated January 31, 2001. Applicants point out to the Examiner that claims 2 and 4 have been cancelled, rendering the rejection of these claims moot. In regards to claims 1, 3, 5 and 6, applicants respectfully traverse this rejection.

The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

Applicants claims as presently amended are directed to an antisense deoxyolignucleotide 8 to 50 nucleotides in length that hybridizes to a target 3′ region of a human thymidylate synthase nucleic acid and that selectively inhibits thymidylate synthase production in human cells. These claimed antisense deoxyoligonucleotides are targeted to the sequences of the 3′ end of the thymidylate synthase RNA. See page 5, lines 8-9 of the Response filed July 2, 2001.

Additionally, the claimed antisense deoxyoligonucleotides are used for cancer therapy in combination with a chemotherapeutic. In particular, the instant antisense deoxyoligonucleotides decrease the growth of cancer cells and have a synergistic, or additive, effect when taken in combination with chemotherapeutics for treating cancer.

In contrast, structurally, Ju does not teach antisense deoxyoligonucleotides in the 3′ region. Ju teaches antisense oligonucleotides, in the form of antisense RNA, targeted at the translation site at the 5′ end of thymidylate synthase mRNA. See page 5, lines 5-6 of the Response filed July 2, 2001. Further, Ju was directed to finding an increased sensitivity with short antisense oligonucleotides but failed to do so and therefore switched to larger RNA antisense oligonucleotides (i.e, teaches away from the inventive subject matter). See page 121, 2nd paragraph, and page 128 of Ju.

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the rejection of pending claims 1, 3, 5 and 6.

2. Rejection of claims 1-2, 5, 8, 9 and 11-12 under 35 USC 112, first paragraph

Claims 1-2, 5 and 8 stand rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Additionally, claims 8-9 and 11-12 stand rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record set forth in the Official Action mailed January 31, 2001.

Applicants point out to the Examiner that claims 2 and 12 have been cancelled, rendering the rejection of these claims moot. In regards to claims 1, 5, 8, 9 and 11, applicants respectfully traverse this rejection.

Claims 1, 5 and 8 stand rejected under 35 USC 112, 1st paragraph for "lack of possession" of the claimed invention. Applicants point out to the Examiner that amended claims 1 and 5 have been narrowed to overcome this rejection. Also, unamended claim 8, by virtue of being dependent from amended claim 5, has thus been narrowed to overcome this rejection.

Claim 1 has been narrowed in scope from an "antisense oligonucleotide" of any length to "an antisense *deoxy*oligonucleotide" which is "8 to 50 nucleotides in length". Claim 1 has been further narrowed from *mammalian* nucleic acid and cells to *human* nucleic acid and cells. Claim 5 combines the narrowed "antisense *deoxy*oligonucleotide" of limited length contained in claim 1 and combines it with an anticancer agent. In view of the significant narrowing of the claims, the instant claims now correspond to the specification as filed. Thus, there is sufficient disclosure contained in the specification to convey possession of the claimed invention.

Claims 8, 9 and 11 stand rejected under 35 USC 112, 1st paragraph for lack of an adequate written description of the claimed invention. In particular, the Examiner has stated that because "the teachings of the specification are purely prophetic, Applicants do not provide sufficient guidance to one

of skill in the art to practice the claimed *in vivo* method based upon *in vitro* examples and prophetic teaching regarding practicing the claimed invention *in vivo*."

Regarding *in vivo* examples, Applicants respectfully remind the Examiner that *in vivo* data is not required under 35 USC §112, first or second paragraph. A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as if in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971); MPEP 2107.01.

The Official Action mailed January 31, 2001 contained the argument (which has been maintained in the present Official Action) that "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate", as per Crooke (1998). Further, the Official Action states "Crooke teaches that variations in cellular uptake and distribution of oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, sequence

of oligonucleotide and cell type." Without conceding the point and reserving the right to pursue this subject matter in additional applications, applicants respectfully point out to the Examiner that the claims have been amended to 1) shorten the length of the oligonucleotide from any length to 8 to 50 nucleotides in length, 2) modified the claimed oligonucleotide to encompass only *deoxy*oligonucleotides, 3) limited the available sequences of claim 3 from seven choices to two choices, and 4) narrowed the present claims to encompass only *human* cells. Therefore, even if the Examiner's position were correct, the level of unpredictability of the inventive subject matter as now recited in the amended claims has significantly decreased.

Further, the Examiner is respectfully reminded that the Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 191USPQ 90, 98 (CCPA 1976). The Examiner has provided no such evidence on *in vivo* methods to applicants. Thus the burden of presenting evidence of unpatentability was not met by the Examiner.

Accordingly, applicants respectfully request the Examiner

to reconsider and withdraw the rejection of pending claims 1, 5, 8, 9 and 11.

CONCLUSION

Based upon the foregoing amendments and remarks, the presently claimed subject matter is believed to be enabled, novel, and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of claims 1, 3, 5, 6, 8-9 and 11 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the pending claims is earnestly solicited.

The Examiner is invited to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

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Appendix A

("mark-up" copy of amended and new claims)

1. (Twice amended) An antisense deoxyoligonucleotide [oligonucleotide] 8 to 50 nucleotides in length that hybridizes to a target 3' region of a human [mammalian] thymidylate synthase nucleic acid and that selectively inhibits thymidylate synthase production in human [mammalian] cells.

3. (Amended) The antisense deoxyoligonucleotide [oligonucleotide] of claim 1 [or claim 2] comprising a sequence according to SEQ ID No 1 or 2 [, 3, 4, 5, 6, or 7].

5. (Amended) A combination product comprising an antisense deoxyoligonucleotide [oligonucleotide] according to claim 1 [targeted to thymidylate synthase] in combination with an anticancer agent.

9. (Twice amended) A method for the treatment of cancer or for providing an antiproliferative effect on cells comprising administering to a human [warm-blooded animal] an effective amount of the combination product claimed in claim 5.

11. (Amended) A method for the treatment of cancer or for providing an antiproliferative effect on cells comprising administering to a human [warm-blooded animal] an effective amount of the antisense deoxyoligonucleotide [oligonucleotide] as claimed in claim 1.

13. (New) The antisense deoxyoligonucleotide according to claim 3, wherein the deoxyoligonucleotide is modified to contain phosphorothiorates, phophotriesters, methyl phosphonates, or short chain alkyl, cycloalkyl or heteroatomic intersugar linkages.

14. (New) The antisense deoxyoligonucleotide according to claim 3, wherein the deoxyoligonucleotide is methoxy-ethoxy winged or contains a peptide nucleic acid backbone.

Appendix B

("clean" copy of amended and new claims)

1. An antisense deoxyoligonucleotide 8 to 50 nucleotides in length that hybridizes to a target 3' region of a human thymidylate synthase nucleic acid and that selectively inhibits thymidylate synthase production in human cells.

3. The antisense deoxyoligonucleotide of claim 1 comprising a sequence according to SEQ ID No 1 or 2.

5. A combination product comprising an antisense deoxyoligonucleotide according to claim 1 in combination with an anticancer agent.

9. A method for the treatment of cancer or for providing an antiproliferative effect on cells comprising administering to a human an effective amount of the combination product claimed in claim 5.

11. A method for the treatment of cancer or for providing an antiproliferative effect on cells comprising administering to a human an effective amount of the antisense deoxyoligonucleotide as claimed in claim 1.

13. The antisense deoxyoligonucleotide according to claim 3, wherein the deoxyoligonucleotide is modified to contain phosphorothiorates, phophotriesters, methyl phosphonates, or short chain alkyl, cycloalkyl or heteroatomic intersugar linkages.

14. The antisense deoxyoligonucleotide according to claim 3, wherein the deoxyoligonucleotide is methoxy-ethoxy winged or contains a peptide nucleic acid backbone.